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Review article

Research gaps identified during the 2014 update of the WHO medical eligibility criteria for contraceptive use and selected practice recommendations for contraceptive use☆

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1. Introduction

Universal access to safe and effective contraception is an important public health goal. Family planning and prevention of unintended pregnancy are essential to securing the well-being and autonomy of individuals, while supporting the health and development of communities [1]. The World Health Organization (WHO) recently undertook a process to update its global guidance on "who" can use contraception safely and "how" to use contraception safely and effectively to generate the fifth edition of the WHO Medical Eligibility Criteria for Contraceptive Use (MEC) and the third edition of the WHO Selected Practice Recommendations for Contraceptive Use (SPR). Overall, the MEC demonstrates that contraception is remarkably safe for most people; at least one highly effective contraceptive method is assigned a category "1" or "2" across the majority of conditions in the guidance, indicating no restrictions on use or that the advantages of using a particular method generally outweigh the theoretical or proven risks of use. Once a medically appropriate method is identified, the SPR offers critical guidance on safe and effective use, important for contraceptive management and service delivery. The major goal for producing these evidence-based recommendations is to help improve access to and strengthen the quality of family planning services worldwide.

While these recommendations reflect a rigorous synthesis and interpretation of the best evidence to date and contribute significantly to medical and public health knowledge around the world, a number of recommendations in both the MEC and SPR are grounded in limited to no direct evidence. Related to safety, conducting research on whether exposure to a contraceptive method would worsen a disease given significant theoretical concerns (e.g., combined hormonal contraceptive use among women with current breast cancer) would be unethical. In other instances, no or very limited published literature directly reports whether or not use of a given method is associated with an important health risk or how best to offer a contraceptive service. In the absence of direct evidence, indirect evidence and expert opinion inform assessments. For example, extrapolating what is known about the safety of contraceptive methods in healthy women to women with medical conditions can be helpful, while taking into account relevant disease processes and how they intersect with what is known generally about the characteristics of methods, associated side effects and potential complications. Even when direct evidence is available, methodological flaws can limit interpretation. The body and certainty of the evidence underpinning the recommendations has increased and improved over time in response to increased and improved contraceptive research.

Each revision of the MEC and SPR offers an opportunity to identify current knowledge gaps and promote research necessary to continually strengthen the guidelines [2]. As part of the most recent revision of these guidelines, a

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Guideline Development Group convened in March and September 2014 to generate updated recommendations. During these meetings, we identified a number of key research questions for a variety of topics discussed during the technical consultations. The full list of research gaps is included in Table 1, not further prioritized. However, we present three important topics of global relevance to national programs and policies in greater detail: (a) intrauterine device (IUD) initiation among women at high risk for sexually transmitted infections (STIs); (b) bidirectional drug–drug interactions with use of hormonal contraception (HC) and antiretroviral therapy (ART); and (c) initiation of progestogen-containing contraception following use of ulipristal acetate (UPA) emergency contraception. Each section presents some background on the public health importance of the topic and discusses the limitations of existing data and considerations for future rigorous research.

2. IUD initiation among women at increased risk for STIs

Women who are at increased risk of STIs may also be at increased risk of unintended pregnancy due to unprotected intercourse, indicating a compelling need for both protection against STIs and effective contraception. IUDs are among the most effective methods of contraception available; however, IUD initiation among women at increased risk for STIs may theoretically increase risk for pelvic inflammatory disease (PID). PID is associated with both acute and long-term severe complications, including sepsis, infertility, ectopic pregnancy and chronic pelvic pain. To better determine the balance of risks and benefits of initiating IUDs among women at high risk for STIs, further research is needed.

The majority of acute PID is caused by STIs, including *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma genitalium* as well as bacterial vaginosis [3]. Untreated lower genital tract infections, most commonly *N. gonorrhea* and *C. trachomatis*, can ascend into the upper genital tract, causing endometritis, salpingitis or other forms of PID; up to 15 to 40% of women with an untreated chlamydial infections or gonorrhea develop PID worldwide [4,5]. Women without STIs undergoing insertion of modern copper-containing and levonorgestrel (LNG)-releasing IUDs is associated with only a small transient risk for PID (9.7 per 1000 women–years) that exists primarily in the first 20 days following placement [6]. More research is needed to determine both best methods to ascertain individual risk for STIs and asymptomatic infection at the time of IUD insertion and whether IUD insertion in the presence of STIs modifies baseline risk for PID.

While there are many epidemiologic risk factors that contribute to the evidence base for STI screening practices, it is unclear whether these same factors, for example, multiple sexual partners, age, previous STI and others, impact the risk of PID with IUD insertion [7–11]. Currently, women at high risk for STIs can be screened for *N. gonorrhea* and *C. trachomatis* if asymptomatic on the day of IUD insertion, followed by later treatment if test results return positive [12]. However, in many parts of the world, STI diagnosis is constrained by a lack of available, easy-to-perform, accurate and inexpensive diagnostic tests. Moreover, there is an urgent need for rapid point of care testing for STIs to allow diagnosis and treatment in a single visit [13]. In areas where laboratory testing is currently unavailable, development and validation of better methods for screening by history or other innovative approaches are also necessary. Strengthened STI surveillance and improved reporting of STI prevalence rates in general populations as well as high-risk subgroups is critical to the larger public health goal of STI control worldwide but also essential for the design and evaluation of potential risk prediction models at the time of IUD insertion [14].

A systematic review prepared as part of the process to generate the third edition of the WHO MEC set out to examine risk for PID among women with STIs at the time of IUD insertion [15]. No studies were identified that directly examined the risk of PID in a group of women with current STIs undergoing IUD insertion compared to no insertion; however, six studies reporting indirect evidence comparing risk for PID among women with and without STIs at the time of copper-bearing IUD insertion were identified. In this report, the absolute risk of PID ranged from 0–5% among women with STIs compared with 0–2% among women without STIs at insertion. An additional study has since been published that retrospectively investigated PID risk among IUD users compared with depot medroxyprogesterone acetate (DMPA) users attending a high-risk urban clinic [16]. Women with a prior history of STIs were more likely to have another STI after insertion but were not more likely to have PID. The incidence of PID was low after IUD insertion (2.2%) and similar to women who received DMPA.

An ideal study to determine if IUD insertion modifies the risk for PID among women with STIs would examine the incidence of PID among women with known STIs who were or were not undergoing IUD insertion. Such a study would not be ethical, as all of the women would have to be followed untreated until they developed PID, unnecessarily exposing them to a serious condition with significant acute and chronic sequelae. Given this challenge, a study comparing the risk for PID among women at high risk for STIs who prospectively undergo IUD insertion versus no IUD insertion offers meaningful, albeit indirect, evidence; however, identifying an appropriate comparison group also poses additional challenges. Because hormonal contraceptives such as combined oral contraceptives (COCs) or barrier methods like the condom or diaphragm may decrease the risk of PID, it is important to take the comparison method into account for future studies. Ideally, information about sexual behavior such as number of partners, frequency of intercourse, age, condom use and other potential confounders should be adequately assessed and controlled for

Table 1
Research gaps identified in the development of the WHO MEC, 5th Edition and SPR, 3rd Edition.

Method	Condition or practice consideration	Unanswered research question
HC	HIV	1. Among women at high risk of acquiring HIV infection who are using HC, compared with women at high risk of HIV infection who do not use a hormonal contraceptive method, to what extent do patterns of condom use explain associations between hormonal contraceptive use and risk of HIV acquisition?
CHC	Breastfeeding	1. Does the use of combined hormonal as compared to non-HC among women who are fully or near fully breastfeeding during the first 6 weeks postpartum affect lactation performance, infant development, infant health or maternal health?
	Postabortion	1. Does immediate use of CHC following a medical or surgical abortion increase the risk of venous thromboembolism (compared to users of non-HC and/or interval initiation)?
CVR	Method initiation	1. How long after the start of the menstrual cycle can a woman initiate use of the combined hormonal vaginal ring without needing to use a backup method of contraception?
POI	HIV	1. Are there differences in behavioral and/or socioeconomic characteristics among women who use injectable contraceptive methods, compared with women who use other contraceptive methods, that modify any associations between contraceptive method use and HIV acquisition risk?
	Method continuation	1. Does the timing of return to fertility after a DMPA subcutaneous injection differ compared with the timing following a DMPA intramuscular injection?
	Problems during use	1. Are there any adverse effects to the woman if DMPA-intramuscular is inadvertently administered subcutaneously?
Implants	HIV	1. Among women at high risk for HIV, is the risk of acquiring HIV infection increased among women who use implants compared with women who use a nonhormonal method of contraception?
	Drug Interactions	1. Does the use of the ARV, EFV, among women using LNG- or ENG-releasing implants decrease the contraceptive efficacy of the LNG- or ENG-releasing implant? 2. Does the concomitant use of antituberculosis medication among women using LNG- or ENG-releasing implants confound any drug interactions between EFV and LNG- or ENG-releasing implants? 3. Does the use of the ARV, Nevirapine, among women using LNG- or ENG-releasing implants decrease the contraceptive efficacy of the LNG- or ENG-releasing implant?
	Obesity	1. Is the effectiveness of Sino-Implant (II) decreased when used by women with increased body weight or body mass index $\geq$30 kg/m^2? Are results from studies conducted among Chinese women reporting on the effectiveness of Sino-Implant (II) with varying values for body mass index generalizable to other populations?
	Method continuation	1. Can Sino-implant (II) be used as an effective method of contraception for more than 4 years? 2. Does the elastomer coating of Sino-Implant (II) affect its biomechanical properties?
IUD	STIs	1. Can an algorithm identify whether risk of acquiring PID is increased with IUD insertion? • Are women with multiple sexual partners at increased risk of PID if they undergo IUD insertion? • Are women who live in a setting with high prevalences of gonorrhea or chlamydia at increased risk of PID if they undergo IUD insertion? • Are there other markers of individual risk for PID that can be used to screen women seeking an IUD insertion?
	Method continuation	1. Does checking for the presence of an IUD string(s) improve user satisfaction with the method? 2. Does checking for the presence of an IUD string(s) increase the method's effectiveness by alerting the user when/if an expulsion has occurred?
ECPs	Breastfeeding	1. Can breastfeeding women safely use UPA for emergency contraception? • To what extent is a breastfed infant exposed to UPA?
	Drug interactions	1. Are there drug interactions between ARVs and emergency contraceptive pills (LNG, UPA or estrogen–progestogen) that decrease the effectiveness of the emergency contraceptive pills? 2. Are there drug interactions between ARVs and emergency contraceptive pills (LNG, UPA or estrogen–progestogen) that decrease the effectiveness of ARVs?
	Obesity	1. Is UPA, compared with LNG emergency contraceptive pills, a more effective method of emergency contraception for women who are obese (30 kg/m^2)?
	Problems during use	1. Is vaginal compared with oral administration of LNG/UPA more or equally effective as emergency contraception?
	Starting a new method after ECPs	1. How long should a woman wait to begin using a regular method of progestogen-containing contraception after she has used UPA for emergency contraception? • Does the effectiveness of UPA decrease when a progestogen-containing method is initiated?
PVR	Breastfeeding	1. Does initiating the use of PVRs in women less than 4 weeks postpartum adversely affect breastfeeding performance, infant health or infant development? 2. Is the contraceptive effectiveness of the progesterone-releasing vaginal ring dependent upon the mother fully breastfeeding? • What is the efficacy of the PVR among women who are practicing limited breastfeeding?

HC = hormonal contraception; CHC = combined hormonal contraception; CVR = combined vaginal ring; POI = progestogen-only injectables; IUD = intrauterine device; ECPs = emergency contraception pills; PVR = progesterone-releasing vaginal ring; HIV = human immunodeficiency virus; STIs = sexually transmitted infections; ARV = antiretroviral medication; UPA = ulipristal acetate; DMPA = depot medroxyprogesterone acetate; LNG = levonorgestrel; ETG = etonogestrel.

in study design and data analysis [17]. Application of standardized criteria for outcome ascertainment of PID is also important to increase interpretation and comparability of results. Studies should also evaluate if any important difference in risk for PID exists for particular subgroups of women according to IUD type, comparing copper and

LNG-releasing devices. Finally, there is a possibility that providers may be sensitized to identify PID in those with an IUD in place; any potential diagnostic bias should be accounted for in study design.

3. Drug–Drug interactions: ART and HC

Sixteen million women worldwide live with HIV — most are of reproductive age, and almost 50% are using ART. For women living with HIV, access to and correct and consistent use of effective contraception is critical to minimizing maternal to child transmission of HIV by preventing unintended pregnancy and to improving health outcomes for these women overall. Some hormonal contraceptives and certain antiretroviral medication (ARV) medications may be subject to drug interactions when used concurrently, potentially leading to uni- or bidirectional decreases in effectiveness or increases in side effects or toxicity of either medication.

The four major classes of antiretroviral medications currently recommended for use in various combination for the prevention and treatment of HIV include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors [18]. The limited existing body of evidence demonstrates great variability in observed pharmacokinetic (PK) interactions among medications within the same ARV class, across classes and according to hormonal contraceptive method, making it difficult to generalize any effects; additional research to better understand any PK or pharmacodynamic (PD) changes and their association with clinical outcomes is needed. NRTIs do not appear to have significant risk for interaction with hormonal contraceptive methods [19]. In contrast, NNRTIs are more likely to induce the hepatic cytochrome P450 family of oxidizing enzymes, particularly CYP 3 A4, responsible for the metabolism of contraceptive steroids, leading to potential interactions with certain HC that may decrease contraceptive effectiveness. Of particular concern is efavirenz (EFV), a potent hepatic enzyme inducer. Regimens containing EFV are recommended by WHO as first-line treatment for adults, adolescents and pregnant and postpartum breastfeeding women as well as those starting ART while on antituberculosis treatment [18].

Existing PK data suggest that EFV leads to decreases in serum concentrations of both ethinyl estradiol and progestogen contained within COCs [20]. Similarly, decreases in hormonal concentrations with concurrent use of EFV and progestogen-only emergency contraceptives have been observed [21]. Furthermore, a small PD study showed higher ovulation rates in women taking EFV-containing ART and COCs [20]. In contrast, other NNRTIs, including nevirapine, etravirine and rilpivirine, do not appear to significantly interact with COCs based on clinical, PK and PD data [22–26]. Based primarily on PK data, the effectiveness of DMPA is unlikely to be affected by NNRTIs, and vice versa, but the potential for combined toxicity in the long term has not been evaluated [27]. No published studies have evaluated ARV drug interactions with norethisterone enanthate.

One retrospective chart review of women using EFV-containing ART reported increased contraceptive failure rates among women using LNG implants. Fifteen of 121 women using EFV (12.4%) became pregnant with a mean time between implant insertion and pregnancy of 16.4 months, while none of the 208 women using nevirapine experienced a failure [28]. Another recently published PK study found that a multidrug ART regimen containing EFV-lowered etonogestrel (ENG) levels among women using ENG implants [29]. While few case reports of contraceptive failure exist in this context, no published comparative studies have evaluated pregnancy rates among ENG implant users during exposure to EFV or other ARVs, and further research is needed to confirm findings among LNG implant users.

Among the studied interactions of PIs and HC, PK data show decreases in COC ethinyl estradiol and progestogen levels with concurrent use of both ritonavir or ritonavir-boosted PIs [30–34]. However, in women using the combined hormonal transdermal patch, co-administration resulted in higher progestogen levels [34]. One study found higher progestogen levels with concurrent PI use in users of progestogen-only pills (POPs), but data on POP levels when used with other ARV classes, such as NNRTIs, are not available. A study of women using ENG implants showed higher ENG levels in women taking ritonavir-boosted lopinavir [29].

Most of the existing data on drug interactions between ARV and HC references PK and PD studies evaluating single agent ARV co-administered with a hormonal contraceptive method. These studies offer indirect but meaningful data, particularly given the paucity of available literature on this topic. An advantage of these studies is that they can typically be completed in a relatively short period of time and require small numbers of participants; however, they can also be resource intensive, requiring inpatient or outpatient facility monitoring and frequent serum sampling for laboratory assays. Typical PK and PD studies include healthy participants. Due to the study design, there can be challenges with recruitment and also ethical concerns related to exposing healthy individuals to potential adverse drug effects associated with unnecessary treatments. While discrete changes can be recorded with single agent co-administration, in reality, women living with HIV are routinely using multiple ARVs that may have interactions with each other and unique interactions with HC. Extrapolating the cumulative PK or PD changes from individual studies of single agent interactions is challenging. Clearly, there is a need to evaluate the PK and PD of common multidrug ARV regimens and HC; however, such studies magnify some of the recruitment and ethical challenges

associated with single agent studies. Further, more information about PK and PD changes at different periods during HC use, such as at initiation, periodic assessment with achievement of steady state concentrations, especially for long-acting methods, and during the hormone-free interval for COCs, patch and ring is important and requires longer follow up to better estimate pregnancy risks and other safety concerns over time.

While PK and PD data can be useful, these results reflect surrogate measures which may not adequately predict important clinical outcomes [35]. Ideally, well-conducted prospective comparative studies reporting on actual contraceptive failures and outcomes related to HIV treatment status offer a better estimation of the true effects of concurrent use by women living with HIV. Given the heterogeneity of effects within ARV drug classes, across classes and by contraceptive method, such an approach to determining the consequences of interactions is not feasible for all potential drug–drug interactions but may be appropriate for investigating those of greatest public health relevance, such as EFV and HC. Due to issues of drug resistance and inadequate treatment, it is not ethical to conduct a trial that would expose women living with HIV to single agent EFV combined with HC, and it would also not be ethical to deny control participants treatment to any ARV or effective HC. However, a pragmatic approach might be an observational study that measures contraceptive failures among women using different multidrug ARV regimens (first line containing EFV vs. second line without) to determine clinically relevant effects. It would be necessary to control for a number of potential confounders that could affect the outcomes of interest, including strict adherence to both the ARV regimen and HC and other factors (e.g., Body mass index) that could have bearing on contraceptive and/or ARV effectiveness. Complicating matters further, women with HIV are also subject to other co-infections, such as tuberculosis; this necessitates treatment with a combination of multidrug ARV regimens and known cytochrome P450 inducers like rifampin, requiring additional investigation. Studies should be conducted in diverse populations of women as responses to medication may vary according to individual characteristics including race, ethnicity, physiology and genetics.

4. Initiating progestogen-containing contraception following use of UPA emergency contraception

UPA has been approved and marketed in several countries as emergency contraception since 2009. It is a selective progesterone receptor modulator effective to 120 h after unprotected intercourse and may delay ovulation up until the peak of the leuteinizing hormone (LH) surge [36,37]. The WHO Guidelines Development Group prioritized the addition of UPA to the emergency contraceptive methods referenced in recommendations for the latest editions of both the MEC and SPR.

To decrease future risk of unintended pregnancy at the time of emergency contraception pill (ECP) use, prompt initiation or continuation of a regular contraceptive method is important. As a selective progestogen receptor modulator, UPA binds to progestogen receptors to delay ovulation, raising theoretical concerns that starting progestogen-containing contraceptives (both progestogen-only and combined hormonal) at the same time as UPA administration may decrease the effectiveness of either the progestogen-containing method, UPA or both. Women, thus, could find themselves at increased risk for both failed emergency protection against unintended pregnancy and incomplete contraceptive protection during subsequent sex acts while using a routine hormonal contraceptive.

There are currently no published studies evaluating any potential interactions reporting clinical outcomes of pregnancy; however, limited PK and PD data are published and reported within the package label for UPA. Results from a study where women used a COC containing ethinyl estradiol 30 mcg and LNG 150 mcg 1 day after administration of UPA during the follicular phase or COC alone demonstrated similar rates of ovulation suppression in both groups, measured by follicle size, serum progesterone and estradiol [38]. This study did not report results from women exposed to UPA alone. Another study examined use of a POP containing desogestrel 75 mcg taken 1 day after UPA during the follicular phase and compared the incidence of ovulation with the use of UPA alone [39]. Even though UPA is rapidly absorbed, a higher incidence of ovulation in the 6 days following desogestrel and UPA intake compared with UPA alone was noted (45% vs. 3%, respectively), and there was also a slower onset of cervical mucus thickening in the group taking desogestrel and UPA compared with the group taking desogestrel alone.

Progestogen-containing hormonal contraceptives rely on various mechanisms of action to confer protection against unintended pregnancy [40]. Not only is it important to understand the effects of coadministration of UPA with all of these methods on intermediate outcomes such as ovulation suppression or cervical mucus thickening, but information on actual contraceptive failure and pregnancy rates is critical. Whether any effect is the same for methods with systemic hormonal exposure (i.e., POP, DMPA, implants) and primarily locally acting methods like the LNG-releasing IUD is also unknown. Knowledge of the duration of any effects following administration of UPA is important to determine the best timing for initiation or continuation of progestogen-containing methods and/or need for and length of required backup protection. For women wanting to start progestogen-containing hormonal contraceptives that they must receive within a clinic setting — such as an implant, LNG IUD or DMPA — it is important to understand these interactions so as to not further burden women with unnecessary delays in initiation and multiple visits to a health care provider.

5. Conclusion

We have elaborated on only a few of the research gaps identified by experts during the updating process to generate the latest editions of the WHO MEC and SPR (Table 1). The highlighted topics and research questions in this article are grounded in this most recent process; however, our commentary is the third in a series of publications promoting diverse areas for research that are critical to better understanding safe and effective contraceptive use [2,41].

Both the MEC and SPR offer recommendations based on the best evidence to date. These guidelines play an important role in ensuring that contraceptive use is restricted with evidence of risk, facilitated when there is evidence of safety, and that effectiveness is maintained through correct and consistent use. Uptake of the recommendations supports quality family planning programs and helps health care providers better serve women and men in their practice. We encourage investigators to consider these research gaps when prioritizing research planning. Results from future high-quality studies in critical areas for research can be incorporated into the evidence base underpinning these recommendations, further strengthening future iterations of these documents while continuing to promote best practices for high-quality family planning care.

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